REMARKS

Claims 1-19 are pending.

Claims 7-15, 18, and 19 have been withdrawn from consideration.

Claim 1 has been amended to add a comma after step a).

Claim 3 has been amended to recite "with a maximum at 18.3 +/- 0.2 degrees 2θ." Support for this amendment is found in the specification at page 5, lines 14-15.

Claims 3, 5, and 17 have been amended to delete the word "about."

Claim 16 has been amended to recite "atorvastatin calcium Form V." Claim 16 has also been amended to recite that the pharmaceutical composition is a solid or suspension. Support for this amendment is found in the specification at page 11, line 2 and page 12, line 8.

The rejection under 35 U.S.C. §112

Claim 16 was rejected for lack of enablement.

This rejection is partly based on a reading of claim 16 that includes solutions of atorvastatin where the pharmaceutically acceptable carrier is water. See the Office Action, page 6, lines 13-16: "Dissolving a specific crystalline form in water, creating an aqueous solution, would put the compound in its free form and not in a crystalline form, with a specific X-ray diffraction pattern."

The Applicants traverse this rejection and submit that:

(1) the plain meaning of the language of claim 16 is being ignored; and

(2) claim 16 is not being interpreted in a reasonable manner in light of the specification.

(1) The Applicants submit that reading claim 16 to encompass solutions where water is the pharmaceutically acceptable carrier is contrary to the plain meaning of the language of claim 16. Claim 16 recites "Form V" of atorvastatin. The specification teaches that Form V is a crystalline form. See, e.g., page 5, line 9: "The new crystalline form of atorvastatin calcium Form V ..." As is well known in the art, and as is pointed out in the quote above from page 6, lines 13-16 of the Office Action, crystalline forms lose their identity upon being dissolved in water. Thus, since claim 16 requires that the pharmaceutical composition comprise "Form V," which is a crystalline form, atorvastatin in solution (where no crystalline form exists) is outside the scope of claim 16. There is no need to enable subject matter that is outside the scope of the claims.

(2) It is well settled that during prosecution claim terms are to be given their broadest reasonable interpretation, but only to the extent that such an interpretation is consistent with the specification. The Court of Appeals for the Federal Circuit has stated that claims must be interpreted in a manner that is consistent with the guidance provided by the teachings of the specification. See In re Morris, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997):

> Since it would be unreasonable for the PTO to ignore any interpretive guidance afforded by the applicant's written description, ... the PTO applies to the verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may

> be afforded by the written description contained in the applicant's specification. [emphasis added]

See also Ex parte Maizel, 27 USPQ2d 1662, 1664 (Bd. Pat. App. & Int. 1993): "[D]uring prosecution the claims are given their broadest reasonable interpretation in light of the specification."

The specification teaches that the claimed crystalline Form V possesses "the advantage of higher solubility in water than atorvastatin Form I" (page 4, lines 21-22). This advantages of the claimed crystalline Form V would be lost in true solutions. An interpretation of claim 16 that encompasses true solutions thus denies the advantages of the present invention to the subject matter of claim 16. Such an interpretation is therefore clearly unreasonable.

Furthermore, page 12, lines 9-11, of the specification states: "[T]he invention is also not intended to pertain to true solutions of atorvastatin calcium whereupon the properties that distinguish the solid forms of atorvastatin calcium are lost." An interpretation of claim 16 that includes true solutions is unreasonable in light of this passage.

Nevertheless, in the interests of expediting prosecution, claim 16 has been amended to recite that the pharmaceutical composition is a solid or suspension. As discussed above, this amendment does not narrow claim 16. Instead, it merely makes explicit what was previously implicit.

This rejection is also partly based on the premise that the act of formulating a pharmaceutical composition comprising Form V would cause a change in crystalline form. See the Office Action, paragraph bridging pages 5 and 6:

> The preparation of the pharmaceutical compositions requires creating solutions, milling, adding diluents, excipients, surfactants, etc. The process of preparing a pharmaceutical composition will cause a specific crystalline form, if in the metastable state, to resort back to the most thermodynamically stable for [sic], which is the form with the lowest vapor pressure. Polymorphs tend to convert from less stable to more stable forms (Rouhi, Chemical and Engineering News, February 24, 2003, pages 32-35, especially page 32).

This stability argument is based on limitations that are not present in claim 16. The Office Action is reading claim 16 as requiring that the pharmaceutical composition defined by claim 16 must:

- contain crystalline Form V for some unspecified (presumably long) time,
- contain some unspecified (presumably high) proportion of crystalline Form V (in relation to the total amount of atorvastatin), and/or
- be prepared by some particular process.

See, e.g., the Office Action at page 7, lines 11-16: "[T]he specification fails to provide the steps of ensuring that the pharmaceutical compositions will maintain the specific forms as found in the specification and will not resort back to the free form or the most thermodynamically stable form of the compound." [emphasis added] See also the sentence bridging pages 8 and 9: "Of [sic] skill in the art would expect the pharmaceutical composition to contain the free form of the compound or the most thermodynamically stable form." See also page 8, lines 6-9: "One of ordinary skill in the art would be unable to maintain a specific metastable crystalline form upon

preparation into a pharmaceutical composition which may require milling or the formation of a solution." [emphasis added]

Claim 16 does not contain any limitations with respect to the crystalline forms maintaining their structure for any particular length of time. The art (e.g., Rouhi, Chem. & Eng. News, February 24, 2003) (Rouhi) teaches that the likely outcome of formulation, when carried out by those skilled in the art, is that the form used would maintain itself for a reasonable period of time such that the pharmaceutical composition would be useful. This is implicit in Rouhi since one of the main themes in Rouhi is that pharmaceutical companies are actively seeking different crystalline forms of compounds (even metastable forms) in order to formulate these crystalline forms into pharmaceutical compositions (see page 32, right column; "[M]uch effort is being expended looking for metastable forms of currently marketed drugs whose stable forms have been around for a long time." It would make no sense for pharmaceutical companies to behave in such a manner if the chances of such metastable crystalline forms disappearing after being formulated were as high as the Office Action contends. Furthermore, Rouhi teaches that the art is aware of the prospect of possible conversion of one crystalline form into another and is well equipped to handle such a prospect. See page 32, right column:

> It is best to work with the most stable polymorph – also called the ground-state form – because it will not convert any further. But the ground state usually is the least soluble. To improve bioavailability, drug companies sometimes trade off polymorph stability with solubility, "recognizing that they will have to deal with the possibility of an undesired conversion to a more thermodynamically stable form ..."

The argument presented in the Office Action implies that claim 16 requires that all of the atorvastatin present in the claimed pharmaceutical composition be the recited crystalline Form V and that there be no atorvastatin present in another form, e.g., the most stable form. See the sentence bridging pages 8 and 9: "Of [sic] skill in the art would expect the pharmaceutical composition to contain the free form of the compound or the most thermodynamically stable form."

To the extent that this rejection is based on such an interpretation, the Applicants submit that the rejection is based on a limitation not present in the claims and is therefore in error. Claim 16 does not require that the pharmaceutical composition contain only Form V and no other form of atorvastatin. It requires a therapeutic amount of the recited crystalline Form V while permitting the presence of other forms, even if those other forms arise via conversion from the recited form. The specification even explicitly teaches that other forms may be present. See page 13, lines 4-6: "Preferred unit dosages of the pharmaceutical compositions of this invention typically contain from 0.5 to 100 mg of the novel atorvastatin calcium Form V, or mixtures thereof with other forms of atorvastatin calcium."

The Applicants believe that the above discussion demonstrates that claim 16 does not lack enablement. In view of the above, it is respectfully requested that this rejection be withdrawn.

The rejection under 35 U.S.C. §102(b)

Claims 1-6, 16, and 17 were rejected as being anticipated by International Patent Publications WO 97/03959 (Briggs) or WO 97/03958 (McKenzie).

The Office Action stated that Briggs disclosed Form II atorvastatin, which has X-ray powder diffraction patterns and ^{13}C nmr chemical shifts "embraced by the instant claimed invention (see especially instant claims 3 and 5)."

Claim 3 has been amended to require a PXRD peak at 5.5 +/- 0.2 degrees 2θ (i.e., between 5.3 – 5.7 degrees 2θ), a PXRD peak at 8.3 +/- 0.2 degrees 2θ (i.e., between 8.1 – 8.5 degrees 2θ), and a broad peak at 18-23 +/- 0.2 degrees 2θ with a maximum at 18.3 +/- 0.2 degrees 2θ (i.e., a broad peak between 17.8-23.2 degrees 2θ with a maximum at 18.1-18.5 degrees 2θ).

Form II of Briggs does not meet these limitations of amended claim 3 because Form II does not have a peak between 8.1 – 8.5 degrees 2θ. Form II also does not have a broad peak between 17.8-23.2 degrees 2θ with a maximum at 18.1-18.5 degrees 2θ. See the table on page 6 of Briggs (reproduced below).

2θ	d	Relative Intensity (>20%) Ground 2 Minutes
5.582	15.8180	42.00
7.384	11.9620	38.63
8.533	10.3534	100.00
9.040	9.7741	92.06
12.440 (broad)	7.1094	30.69
15.771 (broad)	5.6146	38.78
17.120-17.360 (broad)	5.1750-5.1040	63.66-55.11
19.490	4.5507	56.64
20.502	4.3283	67.20
22.706-23.159 (broad)	3.9129-3.8375	49.20-48.00
25.697 (broad)	3.4639	38.93
29.504	3.0250	37.86

Thus, Briggs does not anticipate claim 3.

Claim 1 depends from claim 3. Thus, Briggs does not anticipate claim 1.

Claim 2 is directed to atorvastatin calcium Form V having a PXRD pattern substantially as shown in claim 2. This PXRD pattern is not substantially the same as the PXRD pattern of Form II of Briggs, as the comparison of the pattern shown in claim 2 with Figure 2 of Briggs below demonstrates. Figure 2 of Briggs is the PXRD pattern of Form II.

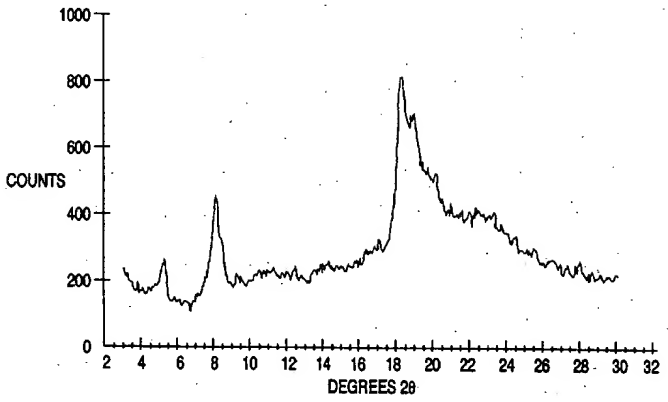
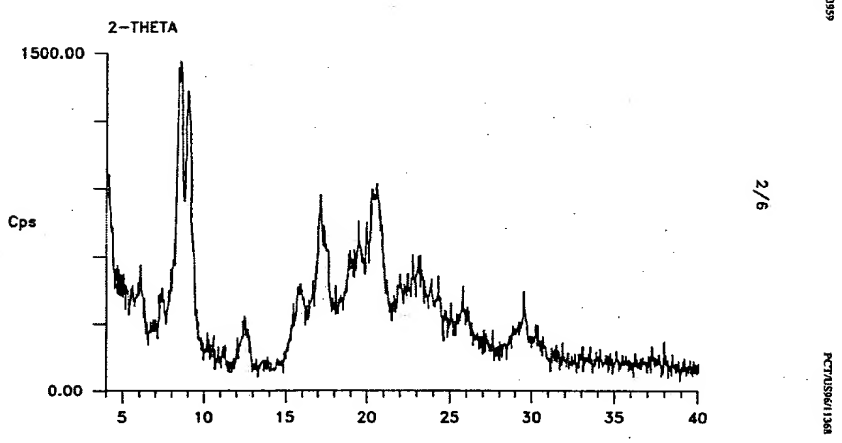
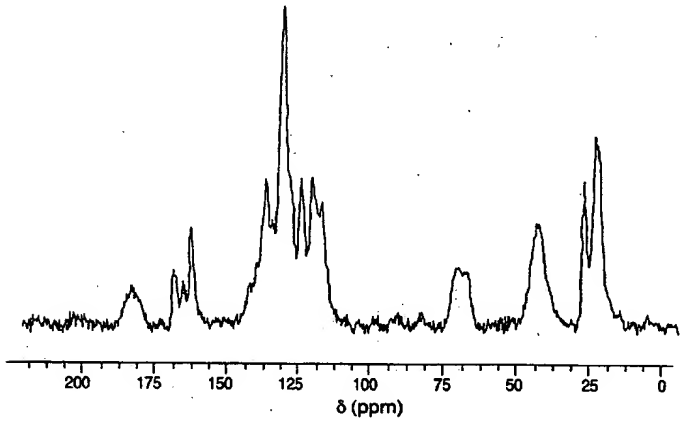


FIG-2

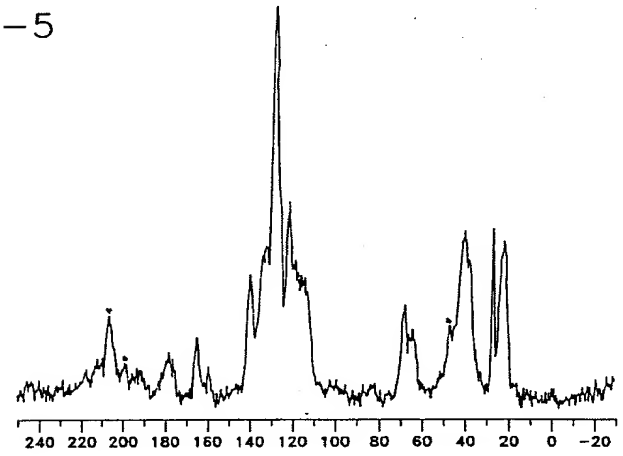


Among the differences between Form V and Form II is the prominent double peak at about 8.5 degrees 2θ in Form II that is the largest peak in the Form II PXRD spectrum. Although Form V possesses a peak in the same general area, the Form V peak is much less prominent and is not the largest peak in the Form V PXRD spectrum. Given this difference, it cannot be argued that the PXRD pattern of Form II is substantially the same as the PXRD pattern depicted in claim 2. Therefore, Briggs does not anticipate claim 2.

Claim 4 is directed to atorvastatin calcium Form V having a ^{13}C NMR spectrum substantially as shown in claim 4. This ^{13}C NMR spectrum is not substantially the same as the ^{13}C NMR spectrum of Form II of Briggs, as the comparison of the ^{13}C NMR spectrum shown in claim 2 with Figure 5 of Briggs below demonstrates. Figure 5 of Briggs is the ^{13}C NMR spectrum of Form II.



FIG–5



Among the differences between Form V and Form II is the difference in the group of peaks between about 150 ppm and 220 ppm. The pattern of these peaks is quite different between these two forms. Given this difference, it cannot be argued

that the ^{13}C NMR spectrum of Form II is substantially the same as the ^{13}C NMR spectrum depicted in claim 4. Therefore, Briggs does not anticipate claim 4.

Claim 5 has been amended to require a ^{13}C NMR spectrum characterized by signals at 21.9, 25.9, 118.9, 122.5, 128.7, 161.0 and 167.1 ppm.

Form II of Briggs does not meet these limitations of amended claim 5 because Form II does not have any of these signals, with the exception of the signal at 161.0 ppm. See the table on page 7 of Briggs (reproduced below).

Assignment	Chemical Shift
Spinning Side Band	209.1
Spinning Side Band	206.8
C12 or C25	181 (broad)
C12 or C25	163 (broad)
C16	161 (broad)
Aromatic Carbons	
C2-C5, C13-C18, C19-C24, C27-C32	140.5
	134.8
	133.3
	129.0
	122.9
	121.4
	120.3
	119.0
	117.1
	115.7
	114.7
C8, C10	70.6
	69.0
	68.0
	67.3
Spinning Side Band	49.4
Spinning Side Band	48.9
Methylene Carbons	
C6, C7, C9, C11	43.4
	42.3
	41.7
	40.2
C33	27.5
C34	22.8 (broad)

Thus, Briggs does not anticipate claim 5.

Claim 6 depends from claim 3 and, since Briggs does not anticipate claim 3, Briggs also does not anticipate claim 6.

Claim 16 depends from claim 1, claim 3, or claim 5 and, since Briggs does not anticipate claim 1, claim 3, or claim 5, Briggs also does not anticipate claim 16.

Claim 17 is directed to Form V characterized by an x-ray powder diffraction peak at 8.3 +/- 0.2 degrees 2θ (i.e., between 8.1 - 8.5 degrees 2θ) and ^{13}C NMR

signals at 21.9, 25.9, 118.9, 122.5, 128.7, and 167.1 ppm. As discussed above in connection with claim 3, Form II does not have a PXRD peak between 8.1 – 8.5 degrees 2θ. As discussed above in connection with claim 5, Form II does not have ^{13}C NMR signals at 21.9, 25.9, 118.9, 122.5, 128.7, and 167.1 ppm. Accordingly, Briggs does not anticipate claim 17.

The Office Action stated that McKenzie disclosed Form III atorvastatin, which has X-ray powder diffraction patterns and ^{13}C nmr chemical shifts "embraced by the instant claimed invention (see especially instant claims 3 and 5)."

Claim 3 has been amended to require a PXRD peak at 5.5 +/- 0.2 degrees 2θ (i.e., between 5.3 – 5.7 degrees 2θ), a PXRD peak at 8.3 +/- 0.2 degrees 2θ (i.e., between 8.1 – 8.5 degrees 2θ), and a broad peak at 18-23 +/- 0.2 degrees 2θ with a maximum at 18.3 +/- 0.2 degrees 2θ (i.e., a broad peak between 17.8-23.2 degrees 2θ with a maximum at 18.1-18.5 degrees 2θ).

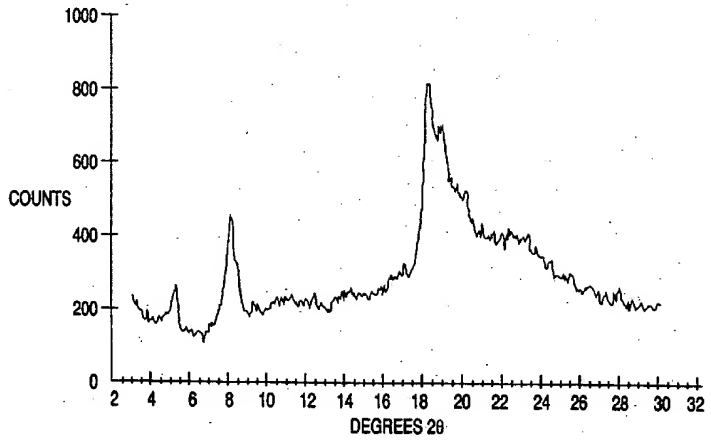
Form III of McKenzie does not meet these limitations of amended claim 3 because Form III does not have a peak between 5.3 – 5.7 degrees 2θ. See the table on page 4 of McKenzie (reproduced below).

2θ	d	Relative Intensity (>25%)
4.123	21.4140	49.20
4.993	17.6832	30.82
5.768	15.3099	28.69
7.670	11.5173	25.49
8.451	10.4538	100.00
15.962	5.5478	32.59
16.619	5.3298	62.34
17.731	4.9981	49.29
18.267	4.8526	45.12
18.870	4.6989	39.52
19.480	4.5531	36.59
19.984	4.4393	70.34
20.294	4.3722	69.54
21.105	4.2061	37.39
21.670	4.0976	36.50
23.318	3.8117	38.63
24.405	3.6442	65.54
24.967	3.5635	27.20
25.397	3.5041	33.75

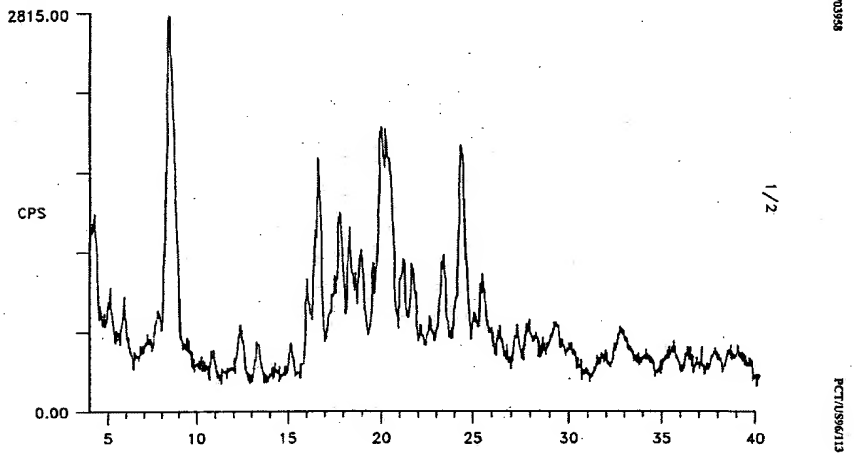
Thus, McKenzie does not anticipate claim 3.

Claim 1 depends from claim 3. Thus, McKenzie does not anticipate claim 1.

Claim 2 is directed to atorvastatin calcium Form V having a PXRD pattern substantially as shown in claim 2. This PXRD pattern is not substantially the same as the PXRD pattern of Form III of McKenzie, as the comparison of the pattern shown in claim 2 with Figure 1 of McKenzie below demonstrates. Figure 1 of McKenzie is the PXRD pattern of Form III.



FIG–1



Among the differences between Form V and Form III is the prominent peak at about 8.5 degrees 2θ in Form III that is the largest peak in the PXRD spectrum. Although Form V possesses a peak in the same general area, the Form V peak is much less prominent and is not the largest peak in the Form V PXRD spectrum. Also noteworthy are the numerous sharp peaks in the 15-19 degrees 2θ area in the Form III spectrum. These peaks are lacking in the Form V spectrum. Given these differences, it cannot be argued that the PXRD pattern of Form III is substantially the same as the PXRD pattern depicted in claim 2. Therefore, McKenzie does not anticipate claim 2.

Claim 4 is directed to atorvastatin calcium Form V having a ^{13}C NMR spectrum substantially as shown in claim 4. This ^{13}C NMR spectrum is not substantially the same as the ^{13}C NMR spectrum of Form III of McKenzie, as the comparison of the ^{13}C NMR spectrum shown in claim 2 with Figure 2 of McKenzie below demonstrates. Figure 2 of McKenzie is the ^{13}C NMR spectrum of Form III.

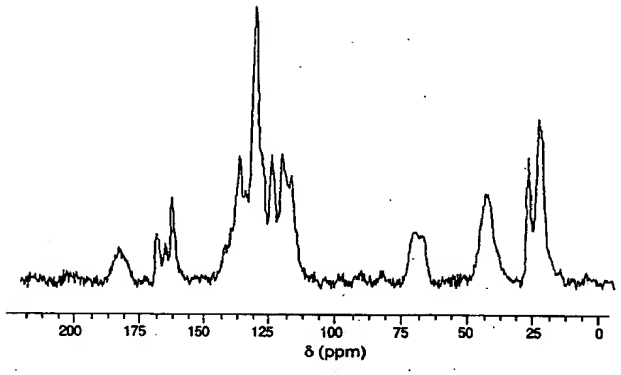
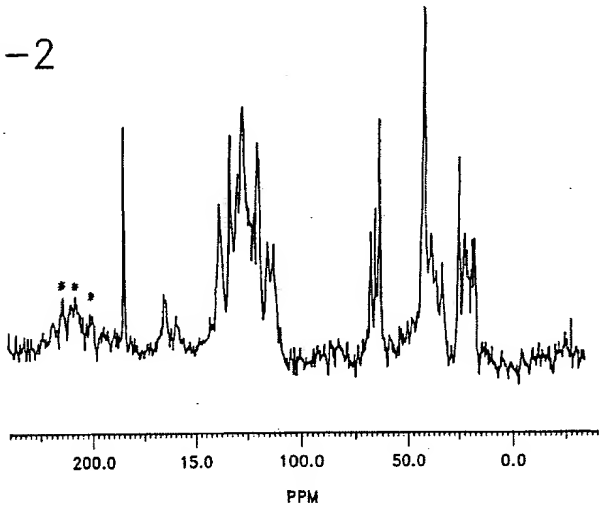


FIG-2



Among the differences between Form V and Form III is the extremely sharp, prominent peak between about 175 ppm and 200 ppm in Form III. Form V has a much less sharp, much less prominent peak in the same general area. Given this

difference, it cannot be argued that the ^{13}C NMR spectrum of Form III is substantially the same as the ^{13}C NMR spectrum depicted in claim 4. Therefore, McKenzie does not anticipate claim 4.

Claim 5 has been amended to require a ^{13}C NMR spectrum characterized by signals at 21.9, 25.9, 118.9, 122.5, 128.7, 161.0 and 167.1 ppm.

Form III of McKenzie does not meet these limitations of amended claim 5 because Form III does not have any of these signals, with the exception of the signal at 161.0 ppm. See the table on page 5 of McKenzie (reproduced below).

Assignment	Chemical Shift
Spinning Side Band	214.8
	209.3
	202.3
C12 or C25	184.9
C12 or C25	166.7
C16	161.0(weak, broad)
Aromatic Carbons	
C2-C5, C13-C18, C19-C24, C27-C32	140.1
	135.2
	131.8
	128.9
	124.3
	122.2
	117.2
	114.9
C8, C10	69.8
	67.3
	65.6
Methylene Carbons	
C6, C7, C9, C11	44.1
	40.4
	35.4
C33	27.0
	24.1
C34	22.1
	19.9

Thus, McKenzie does not anticipate claim 5.

Claim 6 depends from claim 3 and, since McKenzie does not anticipate claim 3, McKenzie also does not anticipate claim 6.

Claim 16 depends from claim 1, claim 3, or claim 5 and, since McKenzie does not anticipate claim 1, claim 3, or claim 5, McKenzie also does not anticipate claim 16.

Claim 17 is directed to Form V characterized by an x-ray powder diffraction peak at 5.5 +/- 0.2 degrees 2θ (i.e., between 5.3 – 5.7 degrees 2θ) and ^{13}C NMR signals at 21.9, 25.9, 118.9, 122.5, 128.7, and 167.1 ppm. As discussed above in connection with claim 3, Form III does not have a PXRD peak between 5.3 – 5.7 degrees 2θ. As discussed above in connection with claim 5, Form III does not have ^{13}C NMR signals at 21.9, 25.9, 118.9, 122.5, 128.7, and 167.1 ppm. Accordingly, McKenzie does not anticipate claim 17.

In view of the above, it is respectfully requested that these anticipation rejections be withdrawn.

The rejection under 35 U.S.C. §103(a)

Claims 1-6, 16, and 17 were rejected as being obvious over Briggs and McKenzie.

This rejection is based on a finding that Briggs and McKenzie disclose crystalline forms of atorvastatin other than Form V (Office Action, page 11, lines 1-7; and page 11, lines 10-11). Motivation to prepare the claimed crystalline Form V would supposedly have come from the expectation of obtaining enhanced properties (Office Action, page 12, lines 6-11). In re Cofer, 354 F.2d 664, 148 USPQ 268 (CCPA 1966) was cited in support of this rejection (Office Action, page 11, lines 14-19).

The Applicants traverse this rejection. It is respectfully submitted that this obviousness rejection relies on hindsight based on the Applicants' disclosure that the claimed crystalline Form V exists. Before the Applicants' invention, Form V was an unknown substance. Moreover, there were no known ways of making Form V. That some other crystalline forms of atorvastatin might have existed does not make obvious the particular claimed crystalline Form V since there could have been no motivation to produce Form V when Form V was not know to exist. Also, there could have been no reasonable expectation of successfully producing Form V when there was no known way of making Form V. Furthermore, the most pertinent case law, including In re Cofer, supports a conclusion that the present claims are non-obvious.

The Office Action stated that the motivation to make the present invention could be found in general knowledge in the art. See the Office Action, page 12, lines 6-11: "One of ordinary skill in the art would be motivated to prepare a different crystalline form of a known compound in the expectation of obtaining that very compound but with enhanced properties, e.g. improved solubility, shelf-life, improved mode of administering properties, etc."

Such "motivation," even if it existed, is not specific enough to provide the motivation necessary to sustain an obviousness rejection of the present claims. Such "motivation" is not directed to Form V, but instead is general, i.e., directed to any pharmaceutical compound. "A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." In re Deuel, 34 U.S.P.Q. 2d (BNA) 1210, 1216 (Fed. Cir. 1995).

This principle of Deuel has been applied in the context of novel crystalline forms of pharmaceutical compounds. In In re Certain Crystalline Cefadroxil Monohydrate, 15 USPQ2d 1263 (U.S. Intern. Trade Comm. 1990), the U.S. International Trade Commission (ITC) reversed a finding of one of its administrative law judges (ALJs) that a Bristol-Myers patent claiming a particular crystalline form of cefadroxil was obvious over two prior art patents that disclosed processes for producing other forms of cefadroxil.

Using reasoning similar to that of the present Office Action, the ALJ based her conclusion of obviousness on a determination that there was a general motivation to find other crystalline forms of cefadroxil and that the claimed crystalline form could have been obtained by methods that were obvious to those of ordinary skill in the art. The ITC summarized the ALJ's reasoning as follows:

> [T]he ID[1] concluded that if these prior art methods were modified in a certain manner, using changes obvious to those with ordinary skill in the art, the Bouzard monohydrate[2] would be produced.

[1] "ID" refers to "initial determination," the name given to the ALJ's report.
[2] The Bouzard monohydrate was the crystalline form of cefadroxil claimed in the Bristol-Myers patent at issue.

In effect, the ALJ concluded that because there was motivation to make a commercially usable form of cefadroxil, and obvious changes to the processes described in the prior art would result in production of the Bouzard monohydrate, which has been commercially successful, the Bouzard monohydrate was obvious under 35 U.S.C. §103. We do not believe that either the ID's inquiries or its conclusions comport with controlling law. The ID's method of analysis is, in fact, identical to that found in the TEO ID, which the Federal Circuit[3] rejected as:

> irrelevant to whether the Bouzard discovery would have been obvious in terms of §103. The question before the Commission was not whether the Bouzard crystal form could have been duplicated with experimentation or with even minor chemical process changes; the question was whether this new crystal form, as a composition of matter, would have been obvious from the teachings of the prior art.
>
> ...
>
> It is insufficient that the prior art shows methods that some (but not all) chemists were able to modify, to produce the Bouzard crystalline form. There must be a suggestion in the prior art that the Bouzard crystal structure would or should be made, whether by manipulation of the Garbrecht or Crast II[4] processes, or by any other process. In factual and legal point is In re Cofer, 354 F.2d 664, 668, 148 USPQ 268, 271 (CCPA 1966), wherein the court held that a new crystalline form of a compound would not have been obvious absent evidence that "the prior art suggests the particular structure or form of the compound or composition as well as suitable methods for obtaining that structure or form."

15 USPQ2d at 1268 [footnotes omitted]

The ITC went on to find the Bristol-Myers patent non-obvious, stressing that the motivation in the prior art was too general, i.e., not directed to the particular

[3] In prior proceedings concerning this dispute, the ITC had denied Bristol-Myers temporary relief (a "TEO") because the ITC concluded that the Bristol-Myers patent was likely to be found invalid for obviousness over the two prior art patents. The Federal Circuit reversed this decision on temporary relief, finding that the Bristol-Myers patent would likely be found non-obvious over the two patents. This Federal Circuit decision was reported at Bristol-Myers Co. v. U.S. International Trade Commission, 15 USPQ2d 1258 (Fed. Cir. 1989) as a non-precedential decision. Thus, this Federal Circuit decision is not binding precedent, although the Applicants believe the reasoning therein is persuasive and would likely be followed again, were the Federal Circuit faced with similar facts.

claimed crystalline structure and that the particular claimed crystalline structure was unpredictable:

> The ID merely determined that motivation existed to produce an improved form of cefadroxil - not the particular structure represented by the Bouzard monohydrate. ... The ID further found that:
>
> > the form of cefadroxil could not be predicted accurately until the experiment was made. Dr. Garbrecht expected that the cefadroxil DMF solvate produced by his '282 patent process would be crystalline, and that the final product of the aqueous crystallization procedure would be a solid, but he had no expectations about the nature of its crystallinity or hydration. (Tr. 342-44.) Dr. Baldwin [a Bristol expert witness] agreed with Dr. Garbrecht, and testified that no chemist could predict the form of hydration that a cefadroxil crystal could take. (Tr. 228.)
>
> Respondents have not disputed or contested this finding. To the contrary, one of their own expert witnesses also testified that he would not have been able to predict in advance the form of the Bouzard monohydrate.
>
> Consequently, the record indicates that the prior art did not and could not have suggested the particular structure and form of the Bouzard monohydrate. Respondents argue that the "predictability" of the Bouzard monohydrate has no relevance to a determination on obviousness, and instead direct our attention to the evidence that they submitted and the ID discussed concerning the obviousness of the modifications to the Crast and Garbrecht patents needed to produce the Bouzard monohydrate. The Federal Circuit, however, has ruled that "predictability" does matter, and that respondents' reliance on the obviousness of changes to prior art processes is in vain ...

15 USPQ2d at 1269-1270 [footnotes omitted]

The facts in the present application are on point with those of In re Certain Crystalline Cefadroxil Monohydrate. The presently claimed crystalline Form V was unknown and its structure was thus unpredictable before the Applicants' invention. The motivation cited by the Office Action is merely general, not directed to the

[4] Garbrecht and Crast II were the two prior art patents.

particular claimed crystalline form. The Office Action relies on the obviousness of changes to prior art processes. These similarities should lead to the same conclusion as in In re Certain Crystalline Cefadroxil Monohydrate – the presently claimed crystalline Form V is non-obvious.

A finding of non-obviousness for the present claims is also mandated by widely applicable principles of obviousness law. The present claims are directed to specific subject matter -- a specific crystalline form of atorvastatin. The motivation referred to in the Office Action is merely a general suggestion to explore the possibility that there may be additional atorvastatin crystal forms in addition to those already known. As explained below, the Court of Appeals for the Federal Circuit has held that such general motivation to explore a new area is insufficient to sustain an obviousness rejection.

In order to arrive at the presently claimed crystalline Form V, based merely on the general motivation referred to in the Office Action, one skilled in the art would have had to vary a large number of parameters in an attempt to find the right parameters for producing Form V. Among such parameters would be: solvent or solvent systems, temperature, time of reaction, atorvastatin concentration, and the nature of the atorvastatin starting material (crystalline, amorphous, hydrated, etc.). All of these parameters would have to be varied independently without any specific guidance from the prior art. It can be readily seen that the number of permutations of these parameters would be enormous, with no guidance from the prior art to narrow down the possibilities.

In view of the lack of specific guidance in the prior art, and the large number of parameters to be varied, the argument provided in the Office Action does not meet the test for adequate motivation to support an obviousness rejection. At most, the argument demonstrates that it might have been "obvious to try" to make the claimed invention. The argument in the Office Action thus falls into the type of obvious-to-try error cautioned against by the Federal Circuit in In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988):

> The admonition that "obvious to try" is not the standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

Furthermore, given the total lack of guidance in the prior art as to the specific reaction parameters that would have led to the claimed crystalline form, the argument provided in the Office Action demonstrates at most that those skilled in the art would have been motivated to explore a promising field of experimentation. Thus, the argument in the Office Action also falls into the second error cautioned against by the Federal Circuit in O'Farrell:

> In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it
>
> 853 F.2d at 903, 7 USPQ2d at 1681.

See also Ex parte Obukowicz, 27 USPQ 2d 1063, 1065 (Bd. Pat. App. & Int. 1992):

> At best, the [cited reference] is but an invitation to scientists to explore a new technology that seems a promising field of experimentation.

> The [cited reference] is of the type that gives only general guidance and is not at all specific as to the particular form of the claimed invention and how to achieve it. Such a suggestion may make an approach "obvious to try" but it does not make the invention obvious.

The Office Action cited In re Cofer, 354 F.2d 664, 148 USPQ 268 (CCPA 1966) in support of the obviousness rejection, stating:

> Changing the form, purity or other characteristic of an old product does not render the novel form patentable where the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art.
>
> Office Action, page 11, lines 14-19.

The Applicants submit that Cofer has been misapplied. In Cofer, the Board of Appeals had sustained a rejection for obviousness of a new crystal form of a compound on the basis of reasoning that closely tracks the reasoning used in the present Office Action. The Board had stated:

> [M]erely changing the form, purity or another characteristic of an old product, the utility remaining the same as that for the old product, does not render the claimed product patentable ...
>
> 354 F.2d at 667, 148 USPQ at 271.

The Court of Customs and Patent Appeals ruled that the broad proposition embodied in the Board's statement was not sound. The Court stated:

The cited cases fail to support the broad proposition that

> * * * merely changing the form, purity or another characteristic of an old product, the utility remaining the same as that for the old product, does not render the claimed product patentable. * * *
>
> 354 F.2d at 667, 148 USPQ at 271.

The Court went on to state that the factors to be given weight in determining whether the claimed crystal form was obvious were whether the particular claimed structure was suggested by the prior art and whether the prior art provided methods of obtaining that structure.

> We think the board failed to address itself to other factors which must be given weight in determining whether the subject matter as a whole would have been obvious, namely, whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form. [emphasis added]
>
> 354 F.2d at 668, 148 USPQ at 272.

Since neither the particular claimed structure, nor methods of obtaining that structure, were disclosed in the art, the Court reversed the rejection for obviousness.

Applying the reasoning of Cofer to the present claims leads to a conclusion of non-obviousness since the prior art suggests neither the particular structure of the claimed crystalline Form V nor methods of obtaining Form V.

Other case law also supports a finding of non-obviousness for the present claims. In In re Irani, 427 F.2d 806, 166 USPQ 24 (CCPA 1970), the Court of Customs and Patent Appeals again reversed the Board of Patent Appeals after the Board held obvious claims to a crystal form of a compound based on a disclosure of a non-crystal form of the same compound. The Court found that the prior art did not suggest that the particular claimed crystalline compound existed or provide a method for making it.

> Upon due consideration of all these reference disclosures concerning the physical forms in which various known aminophosphonic acids exist, we think the most definite conclusion that can be reached is that

> some of these acids can be obtained in crystalline form and some cannot, and that of the former group some can be obtained with ease by conventional procedures and some only with great difficulty by specially devised techniques. This being the case, we cannot conclude that it would have been obvious that crystalline, anhydrous ATMP could exist.
>
> As stated above, even assuming that one skilled in the art could have predicted with reasonable certainty that crystalline anhydrous ATMP could be produced, we are not convinced by this record that it would also have been obvious *how* this could be achieved. We note that neither the examiner nor the board has contended that a suitable process would have been obvious. [italics in original]
>
> 427 F.2d at 809, 166 USPQ at 27.

The present situation is similar to that in Cofer and Irani. The prior art fails to suggest the existence of the particular claimed crystalline form and the prior art fails to suggest methods by which that particular crystalline form can be obtained. Given the holdings in Cofer and Irani, it is clear that the present claims, like those in Cofer and Irani, are not obvious.

The lack of disclosure of a method of making the claimed crystalline form in the prior art leads to a conclusion of non-obviousness for the present claims not only under Cofer and Irani but also under In re Grose, 201 USPQ 57 (CCPA 1979). In Grose, the court made it clear that a conclusion of obviousness of one compound based upon its structural similarity to another compound depends upon the assumption that the method disclosed for producing the prior art compound can be used to produce the new compound.

> One of the assumptions underlying a prima facie obviousness rejection based upon a structural relationship between compounds, such as adjacent homologs, is that a method disclosed for producing one

> would provide those skilled in the art with a method for producing the other.

201 USPQ at 63.

> Failure of the prior art to disclose or render obvious a method for making any composition of matter ... precludes a conclusion that the composition would have been obvious.

201 USPQ at 64.

There is no evidence of record that shows that the presently claimed crystalline Form V can be produced by the methods disclosed in the prior art. The production of particular crystalline forms of atorvastatin is highly sensitive to the precise reaction conditions used. The use of different reaction conditions, such as different solvents or different temperatures, leads to the production of different crystalline forms of atorvastatin.

Even the use of mixtures of methanol and water can lead to the production of different forms of atorvastatin, depending on ratio of methanol and water as well as the choice of other conditions such as temperature of incubation. For example, Briggs used a mixture of methanol:water (3:2) and stirred for three days at an unspecified temperature to produce Form II (see Example 2, page 27, lines 20-30). The present application also discloses the preparation of Form V from a mixture of methanol:water (4:3) that was heated to 60°C and then cooled to between 10°C and 15°C within 3 hours. Form V could also be produced from a 1:1 mixture of methanol and water at room temperature (see the present application, Example 3, page 15) or from a 4:3 mixture of methanol and water at 45°C (see the present application, Example 4, page 15).

Given that the production of a particular crystalline form of atorvastatin is highly sensitive to the precise reaction conditions used, it is highly unlikely that the prior art methods would produce the presently claimed crystalline Form V. Accordingly, the presently claimed crystalline Form V is non-obvious under Grose.

The current rejection is inconsistent with well-established principles relating to the obviousness of chemical compounds. It is well settled that the properties of a claimed chemical compound must be taken into account when conducting an obviousness inquiry. See, e.g., In re Papesch, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963): "From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing." The Grose court reiterated this principle and stated that differences in X-ray diffraction patterns between a claimed compound and prior art compounds were among the types of differences in properties that support a conclusion of non-obviousness for claimed compounds.

> Determining whether a chemical composition is prima facie obvious from another may rest on whether differences in structure and properties of the compositions can be accounted for by obvious modifications in the synthesis process or by obvious modifications of one composition to yield the other. If the differences in X-ray diffraction data between the zeolites here involved had indicated an actual difference in crystal structure, the present record would belie a conclusion that such differences resulted from obvious modifications of any prior art synthesis process or from obvious modifications of Milton's zeolite R to yield the claimed zeolite.
>
> 201 USPQ at 63.

The X-ray diffraction pattern of the claimed crystalline Form V differs from the X-ray diffraction patterns disclosed in the prior art. These differences represent real, significant differences in structure, and thus properties, between Form V and prior art forms. "Because of differences in the dimensions, shape, symmetry, capacity (number of molecules), and void volumes of their unit cells, the different polymorphs of a given substance have different physical properties arising from differences in molecular packing." David J. W. Grant, *Theory and Origin of Polymorphism,* in Drugs of the Pharmaceutical Sciences, vol. 95, Polymorphism in Pharmaceutical Solids, Chapter 1, sentence connecting pages 5 to 8 (Harry G. Brittain ed., 1999).[5] Physical properties that may differ among various polymorphs include: packing properties, thermodynamic properties, spectroscopic properties, kinetic properties, surface properties, and mechanical properties. *Id.* at 7. Because different crystalline forms exhibit different structure and different properties, the disclosure of one crystalline form of atorvastatin does not render obvious another crystalline form of atorvastatin. The different structures and different properties of crystalline forms make this art unpredictable. There is a large amount of uncertainty involved in arriving at any particular crystalline form of atorvastatin, or even knowing that such a form exists. The process of making new crystalline forms is essentially a process of trial and error. See, e.g., Rouhi, Chem. & Eng. News, February 24, 2003, pp. 32-35, at p. 32: "But no method yet exists to predict the polymorphs of a solid compound with significant certainty. The search for polymorphs is largely an empirical exercise." The Patent Office has recognized this unpredictability by routinely

[5] A copy of this publication is provided with the Supplemental Information Disclosure Statement accompanying this Amendment.

granting patents for novel crystalline forms over both the free form and other known crystalline forms. *See, e.g.,* U.S. Patent No. 6,605,729.

The present claims are not obvious over Briggs and McKenzie because the disclosures of Briggs and McKenzie fail to provide a reasonable expectation of success for the present claims. Because there is a large amount of uncertainty involved in arriving at any particular crystalline form of atorvastatin, or even knowing that such a form exists, a prior art disclosure of a particular crystalline form of atorvastatin does not make obvious any other crystalline forms. The process of making new crystalline forms is essentially a process of trial and error. See, e.g., Rouhi (discussed above).

Moreover, the Office Action is mistaken in assuming that the claimed crystalline Form V does not possess superior properties. The claimed crystalline Form V has higher solubility in water than Form I. See page 4, lines 20-21. For this reason, too, the present claims are non-obvious.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Withdrawn claims

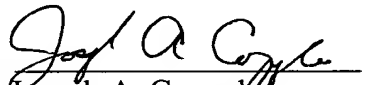
The Applicants respectfully request rejoinder of the withdrawn claims.

Claims 7-15, 18, and 19 are process claims that depend from product claims 2-5. As discussed above, claims 2-5 are allowable. Therefore, rejoinder is proper.

The time for responding to the Office Action was set for November 1, 2005. Enclosed is a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this response.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully submitted,

By 
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